Translation

PATENT COOPERATION TREA

PCT/EP2003/006509

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B38209PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP2003/006509	International filing date (*day/month/year*) 20 June 2003 (20.06.2003)	Priority date (*day/month/year*) 20 June 2002 (20.06.2002)
International Patent Classification (IPC) or national classification and IPC C12N 5/00		
Applicant BIONETHOS HOLDING GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 8 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19 January 2004 (19.01.2004)	16 November 2004 (16.11.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/EP2003/006509

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:

pages 1-22, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages _____, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 1-34, filed with the letter of 08 September 2004 (08.09.2004)

☐ the drawings:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-34 (in part)

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-34 (in part) are so unclear that no meaningful opinion could be formed *(specify)*:

SEE SUPPLEMENTAL SHEET

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

1. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1.1 Contrary to PCT Article 6, the claims are not supported by the description because their scope goes beyond the scope justified by the description and the drawings. The claims relate to a large number of possible combinations of growth factors, yet the application provides support by the description (PCT Article 5) and disclosure (PCT Article 6) only for a limited number of these combinations, namely compositions comprising thrombopoietin (TPO), erythropoietin (EPO) and/or growth hormone (GH).

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-6, 11, 12, 14-18, 21-25, 27, 28, 29, 31, 33, 34	YES
	Claims	7-10, 13, 19, 20, 26, 30, 32	NO
Inventive step (IS)	Claims		YES
	Claims	1-34	NO
Industrial applicability (IA)	Claims	1-34	YES
	Claims		NO

2. Citations and explanations

This report makes reference to the following documents:

D1: ASAKAWA, K. ET AL.: 'HUMAN GROWTH HORMONE STIMULATES LIVER REGENERATION IN RATS', Journal of Endocrinilogical Investigation, 1989, Vol. 12, No. 5, pages 343-347

D2: WO 96 27657 A (MASSACHUSETTS INST TECHNOLOGY), 12 September 1996 (1996-09-12)

D3: WO 01 48153 A (CHILDREN'S MEDICAL CENTER), 5 July 2001 (2001-07-05)

D4: WO 90 10647 A (UNIV CALIFORNIA), 20 September 1990 (1990-09-20)

D5: US-A-5 919 702 (PURCHIO ANTHONY F ET AL), 6 July 1999 (1999-07-06)

D6: RATAJCZAK J ET AL: 'IMPROVED SERUM FREE SYSTEM FOR CLONING HUMAN PURE ERYTHROID COLONIES. THE ROLE OF DIFFERENT GROWTH FACTORS AND CYTOKINES ON BFU-E FORMATION BY THE BONE MARROW AND CORD BLOOD CD34+ CELLS', FOLIA HISTOCHEMICA ET CYTOBIOLOGICA, VESALIUS UNIVERSITY MEDICAL PUBLISHER, KRAKOW, PL, Vol. 36, No. 2, 1998, pages 55-60, XP000886615, ISSN: 0239-8508

2.1 Document D1 describes the use of GH to produce a

preparation for promoting liver regeneration (see table 1). In view of the teaching in D1, a person skilled in the art would consider the use of GH to produce a medicament for treating all kinds of liver diseases obvious. Consequently, the subject matter of **claims 1-5** does not involve an inventive step. The use as per **claim 6**, according to which a support structure coated with GH is used, cannot be considered inventive either, since the use of support structures coated with growth factors has already been disclosed in the prior art (see D2) and a person skilled in the art would therefore regard the use of the support structures coated with GH known from D1 to promote liver regeneration as a conventional alternative.

2.2 Document D2 describes compositions comprising a support structure (see page 5, line 5 - page 11, line 2; page 10, line 20 - page 11, line 2; page 12, line 25 - page 13, line 4) coated with growth factors (in particular EPO, TGF-beta and PDGF). The compositions can be used for cultivating cells and tissues both *in vivo* and *in vitro* (see page 3, lines 25-28; page 14, lines 18-20; and page 15, line 1 - page 20, line 8), and are especially suitable for promoting the growth of liver cells (see example 1). The compositions described in D2 can contain at least one growth factor from each group of growth factors, as listed in claims 8-11 (EPO from the group mentioned in claim 1, TGF-beta from the group mentioned in claim 2, and PDGF from the group mentioned in claim 3). Since the growth factors can be used alone or in combination (see page 12, lines 25-27), the teaching in D2 anticipates the method for *in vitro* regeneration of liver cells, in that

EPO (**claims 7 and 8**), EPO and TGF-beta (**claims 7 and 9**) or EPO, TGF-beta and PDGF (**claims 7 and 10**) were used. That document also anticipates the biological matrix containing the growth factors (**claim 20**), as well as the method for producing a biological matrix (**claim 26**), the device for carrying out the method as per claim 1 (**claim 30**) and the use of growth factors to produce a medicament for the therapeutic regeneration of tissues (**claim 32**).

2.3 All other embodiments of the invention mentioned in the dependent claims relate to simple variations of the methods and devices in the independent claims which require only general knowledge and routine laboratory procedures for their development. Consequently the subject matter of **claims 1-6, 12-19, 21-25, 27-29, 31, 33 and 34** does not involve an inventive step (PCT Article 33(3)). The claims would only be acceptable if they related to a novel and inventive independent claim. The method for reproducing cells in the presence of endothelial cells (claim 4) cannot be considered inventive either because a person skilled in the art knows from document D3 that a support structure can be populated with endothelial cells in order to promote the reproduction of other cells. A person skilled in the art would therefore include endothelial cells in the method of D2 and would arrive at the subject matter of **claim 11**.

2.4 D4 describes a method for promoting the growth of nerve cells, in which ciliary neurotrophic factor (CNTF) is adsorbed on nitro-cellulose paper or on a prosthesis (see page 7, lines 8-11) and the CNTF-coated support structure is implanted in the brain

as a neural bridge (page 7, lines 13-37). That document anticipates the claims directed to the biological matrix and its uses insofar as they relate to the use of a single growth factor (CNTF) (**claims 20, 26, 30 and 32**). In view of the disclosure in D4, the claims dependent on claims 8, 21, 26, 30 and 32 do not involve an inventive step for the reasons explained in point 2.2.

2.5 D5 discloses a method for regenerating cartilage by growing chondrocytes in a 3D matrix coated with growth factors (column 6, lines 43-59). TGF-beta, IGF-I, IGF-II, GH or BMP are preferably used as growth factors (see column 3, line 47 - column 5, line 44). That document anticipates the claims directed to the biological matrix and its uses insofar as they relate to the use of a single growth factor (GH) (**claims 20, 26, 30 and 32**). In view of the disclosure of D4, the claims dependent on claims 20, 26, 30 and 32 do not involve an inventive step for the reasons explained in point 2.2.

2.6 D6 presents a method for promoting the growth of erythroid precursor cells from bone marrow or umbilical cord blood CD34+ cells, the cells being stimulated with a composition of EPO and GM-CSF or EPO and NGF. That document anticipates the claims insofar as they relate to the device for carrying out the method as per claims 1 and 2 (**claim 30**) and to the use of the growth factor EPO to produce a medicament for the therapeutic regeneration of tissues. D6 is not prejudicial to the novelty of the claims that relate to the biological matrix or to the method for producing the same.

2.7 Moreover, the totality of the teaching in the application cannot be considered inventive because it is not certain whether the invention can be carried out over the entire scope of the claims. Claims 1-10 relate to so many growth factors that they encompass hundreds of possible growth factor combinations. The application shows results only for an indeterminate mixture of TPO, EPO and/or GH, which is not considered to be a sufficient disclosure to make all possible combinations for solving the problem in question acceptable. This objection could be overcome only if the claims were restricted to particular growth factor combinations and if the combinations showed an unexpected effect and were supported by the originally submitted application.

Further observations on the international application

2.8 The description (examples 1-5) indicates that the growth process can be locally initiated and terminated and structurally guided only by a biological matrix (page 8, lines 20-22). The use of a biological matrix or support structure in the cell reproduction method is therefore necessary for the definition of the invention (see also examples 1-4). Since independent claims 1 and 7 do not include this feature they do not meet the requirement of PCT Article 6 in conjunction with PCT Rule 6.3(b), according to which each independent claim must include all the technical features that are necessary for the definition of the invention.

2.9 Dependent claim 16 relates to different embodiments of the biological matrix. The claim is dependent not

only on claims that relate to methods by which the cell growth process is initiated by a biological matrix but also on claims which do not mention the matrix or a support structure. This results in a lack of clarity because a dependent claim cannot define a feature that is absent from the independent claim.

2.10 The characterising feature in claim 5 is already found in the characterising part of the independent claim.